Pink urine and a petechial rash

Hector M Ramos
Richard Bertken
David R Pepper
University of California, San Francisco
Fresno Family Practice Program
445 S Cedar Ave
Fresno, CA 93702-2907

Correspondence to:
Dr Ramos
hector.ramos@ucsfresno.edu

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QUESTIONS: A 52-year-old Hispanic woman with a long history of bilateral knee pain and type 2 diabetes mellitus sees her family physician because in the past 4 days she has had pink urine, generalized malaise, and a rash on her hands and feet.

On physical examination, the patient has oral and lingular submucosal hemorrhages (figure 1), injected sclerae with subconjunctival bleeding, and tenderness of both knees. She also has a vesiculomacular rash with a dark erythematous base that is clustered and more severe on her legs than on her arms (figure 2). She has sparse pinpoint macular lesions on her torso. Her temperature is 38.3°C (101°F), and she has a new ejection systolic murmur at the left upper sternal border. On reexamination several hours later, the number of lesions on her legs has increased.

What additional questions would you ask this patient, and what other parts of the body would you examine? What kind of skin lesions are these, and what is your differential diagnosis? What tests would help make the diagnosis? What is the diagnosis, and how would you treat it?

Figure 1 Submucosal hemorrhages and diffuse petechiae on oral and lingular surfaces

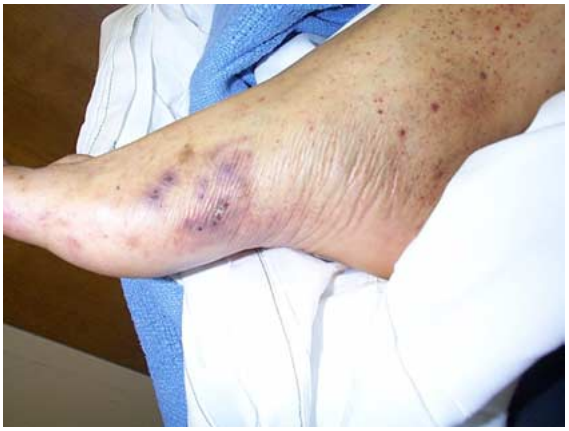

Figure 2 Vesiculomacular rash with a dark erythematous base

ANSWERS

Additional history

A key part of the history was the patient's medicine list, which included rofecoxib (Vioxx), metformin, glyburide, levothyroxine sodium, hydroxychloroquine sulfate, and a short course of prednisone. Therefore, important questions to ask are, "What medications are you taking?" and "Have you had fever, chills, or night sweats?" Several medications can cause rash or other idiopathic reactions, and thus, a detailed history of medication use is important—sulfa-containing antibiotics are particularly likely to cause a rash.[1(p43)] The presence of fever, chills, and night sweats may indicate an underlying infectious cause.

Additional physical examination

The patient's spleen should be examined to evaluate its size. A large spleen could be a sign of leukemia or lymphoma. The neck should also be examined for meningism. Although this diagnosis is unlikely in this particular case, missing meningococcal septicemia would be catastrophic.

Skin lesions

The patient's skin lesions were a mixture of petechiae and purpura. Petechiae are discrete, flat (macular), small (1-2 mm), round lesions that originate from capillary bleeding. In places, these can cluster to form larger lesions. Purpura are larger submucosal hemorrhages (see photograph of tongue).

Differential diagnosis

Fever in a patient who has a rash can be due to systemic fungal, bacterial, and viral infections or to inflammatory and immune conditions (see this article on our web site for a link to more information about causes of fever in patients with a rash).[2(pp63-66,254,259),3]

Important investigations

To arrive at a diagnosis from the long list of differential diagnoses, important tests are those that evaluate the blood components and clotting, those that look for infection and sepsis (including disseminated intravascular coagulation), and those that look for autoimmune disease.[2]

In our initial investigations, the urinalysis showed moderate amounts of protein, red blood cells, and white blood cells. Her metabolic profile was normal. Her erythrocyte sedimentation rate was 131 mm per hour. A complete blood cell count revealed thrombocytopenia (platelet count, 17×10^9/L [17×10^3/μL]); white blood cell count, 5.8×10^9/L (5,800/μL); hemoglobin, 110 g/L (11 g/dL);

and hematocrit, 0.34 (34%). Her platelet count 12 hours later was 4 × 10^9/L. Her prothrombin and partial prothrombin times and results of a D-dimer test were all normal, but a total bilirubin level was 31 μmol/L (1.8 mg/dL), with an indirect bilirubin of 22 μmol/L (1.3 mg/dL), indicating mild hemolysis. An echocardiogram identified mild mitral regurgitation, mild aortic insufficiency, an ejection fraction of 65%, and no vegetations. Her murmur was most likely related to flow and not a pathologic disorder.

The patient had a positive reaction to antinuclear antibodies (a screening test for connective tissue disease) with a titer of 1:640 (reference, <40) and a homogeneous pattern. She also had elevated levels of antibodies to double-stranded DNA (40; reference, <10) and other more specific antibodies (anti-sm, 42 [reference, <5], SS-A, 84 [reference, <3], and SS-B, 95 [reference, <3]).

Diagnosis

The combination of the high titers of antinuclear antibodies, subtype DNA antibodies and a specific pattern of fluorescent staining is found exclusively in patients with active systemic lupus erythematosus (SLE).[4(pp62-66)] She also had a positive reaction to antiplatelet IgG antibodies (anti-IgG direct Ab). Antibodies that attack platelets are either autoantibodies (eg, drug-induced or in chronic idiopathic thrombocytopenic purpura) or from a foreign platelet antigen (eg, after transfusion).[4(p406)]

Treatment

Initial treatment included triple empiric intravenous antibiotic therapy with ampicillin, gentamicin sulfate, and nafcillin sodium for the first day to cover the most lethal organisms until blood culture results were available. The patient was given 6 units of platelets, and a regimen of high-dose steroids—initially intravenous methylprednisolone sodium succinate (Solu-Medrol), 125 mg every 6 hours, then tapered to oral prednisone, 60 mg a day—and intravenous gamma globulin was started to reduce the inflammation caused by an active autoimmune process.

Two distinct subsets of thrombocytopenia occur in patients with active SLE.[5] The less severe type presents with a platelet count that ranges between 40 and 120 × 10^9/L; is rarely associated with bleeding other than minor petechiae, purpura, or bruising; and other active SLE findings are absent. This condition usually requires only small doses of steroids or no treatment at all.[5] However, patients with refractory (more severe) thrombocytopenia in which the platelet count abruptly falls below 20 × 10^9/L and with signs of active bleeding may require substantially higher doses of corticosteroids and cytotoxic drugs or intravenous gamma globulin to stop the fall in the platelet count.[5] However, no good research has been done on the efficacy of these therapies.[5]

A rheumatologist was consulted who recommended stronger immunosuppressive therapy, and a single dose of cyclophosphamide, 1 g/m^2, was given over 1 hour with ondansetron hydrochloride, 32 mg intravenously, to prevent nausea; this regimen was continued in the outpatient setting.

Outcome

The patient responded well to this initial therapy, and after the fourth hospital day the submucosal bleeding had stopped. Her laboratory test results indicated that SLE was the likely cause of rash, nephritis, and thrombocytopenia. Although unlikely, one of her medications may have contributed to activating this illness. She continued to recover and required fewer platelet transfusions. Her symptoms continued to resolve, her platelet count stabilized, and she was discharged to home without complications after 10 days.

After discharge, the patient developed Cushing syndrome due to the prolonged prednisone use, but she has not required any further platelet transfusions or hospitalizations. Because she declined to have a renal biopsy, the type of nephritis could not be confirmed.

SLE

Systemic lupus erythematosus has many clinical manifestations, including fatigue, fever, malaise, and weight loss.[2] Cutaneous findings include rash from photosensitivity, vasculitis, alopecia, or oral ulcers. Arthritic symptoms can be symmetric or nonerosive. Hematologic findings include anemia, neutropenia, thrombocytopenia, lymphadenopathy, splenomegaly, and venous or arterial thrombosis. This disorder can affect any organ and includes pleuritis, pericarditis, myocarditis, endocarditis, nephritis, peritonitis, vasculitis, and cerebritis.[6]

Systemic lupus is an autoimmune disease characterized by the presence of various autoantibodies that bind to DNA, nuclear antigens, and ribonucleoproteins. Deposition of immune complexes in most organs will cause damage to those tissues. Like other autoimmune conditions, the cause of SLE is multifactorial, involving genetic, environmental, hormonal, and immunologic factors.[5]

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